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Review article

Targeting aberrant cancer metabolism – The role of sirtuins

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ABSTRACT

Cancer cells, as opposed to normal cells, generate energy by increasing aerobic glycolysis, which is a phenomenon called "the Warburg effect". An altered energy metabolism supporting continuous cell growth and proliferation was pointed to as the new "hallmark" of cancer cells. Several hypotheses have been proposed to explain the maintenance of this seemingly wasteful catabolic state. The epigenetic mechanisms which depend on the covalent modifications of both DNA and histones have recently emerged as important players in the regulation of glucose metabolism. The sirtuin family of histone deacetylases has emerged as important regulators of diverse physiological and pathological events, including cancer metabolism. Sirtuins 1–7 (SIRT1–7) belong to class III of histone deacetylase enzymes which are dependent on NAD^+ for activity. It was recently demonstrated that SIRT6 is a tumor suppressor that modulates aerobic glycolysis by repressing HIF1 transcription. Members of this family of enzymes are considered promising pharmaceutical targets for cancer treatment. This review highlights the major functions of sirtuins in relation to cancer metabolism and the possibilities of their activation and inhibition by small molecule drugs.

Contents

Abbreviations: CAC, citric acid cycle; ROS, reactive oxygen species; SIRT, sirtuin; STACs, sirtuin-activating compounds.

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Introduction

Q2 The fundamental feature of tumor cells is uncontrolled proliferation. A rich body of knowledge has been gained in the past few decades regarding the molecular mechanisms of this phenotype change. According to the somatic mutation theory, tumorigenesis appears to result from random genetic and/or epigenetic changes, and is described as "an unidirectional process which occurs in a stepwise manner" [1]. However, a close examination of the various models of tumorigenesis reveals that a unified concept of the origin of cancer has not yet emerged, despite intense efforts to integrate the wealth of disparate data that has accumulated over the past several decades. Among the alternative theories which may reframe the classical paradigm of carcinogenesis, those which take into consideration the formation of cancer stem cells and the involvement of the cell microenvironment are the most promising [2,3]. Irrespective of the explanatory utility of these theories, one of the most intriguing features of cancer cells is the appearance of aerobic glycolysis, known as the Warburg effect.

This phenomenon, which was first observed by Otto Warburg in the 1920s, was initially thought to be adaptation to hypoxic conditions, but later studies showed that the mutations that lead to tumorigenesis also cause aerobic glycolysis by up-regulating the expression of glycolytic genes at the transcriptional level [4]. The Warburg effect seemed to be incompatible with the concept of the stepwise evolutionary progression of normal cells to cancer cells. This is because aerobic glycolysis is very inefficient when it comes to energy generation, and by producing lactate it also causes an acidic environment that is unsuitable for cell proliferation. Therefore, it was assumed that it cannot confer rapid proliferation and provide a selective advantage to cancer cells. However, it is now widely accepted that the Warburg effect is in fact one of the key features of tumorigenesis [5]; it not only promotes rapid uncontrolled proliferation but also confers invasive properties. Indeed, solid tumors often exhibit areas of hypoxia and acidosis [6], which stimulate angiogenesis and further augment tumor growth. Analyses based on evolutionary game theory and systems biology also point to the importance of the Warburg effect in tumorigenesis [7]. We have come a long way in realizing that cancer cells cannot do away with aerobic glycolysis [8], and the Warburg effect has been proposed as a fundamental property of tumor cells rather than as the consequence of malignant transformation.

Several hypotheses have been proposed regarding the maintenance of this seemingly wasteful catabolic state. Recent investigations of the mechanisms that underlie the Warburg effect suggest that: (1) mitochondrial uncoupling can promote aerobic glycolysis in the absence of permanent and transmissible alterations to the oxidative capacity of cells; (2) aerobic glycolysis may represent a shift to the oxidative metabolism of non-glucose carbon sources, *e.g.* particularly glutamine, which is an amino acid that is ultimately converted to α-ketoglutarate in the mitochondria in order to enter the citric acid cycle (CAC) [9]; and (3) mitochondrial uncoupling may be associated with increased resistance to chemotherapeutic insults [10].

Besides the hypotheses that suggest the direct involvement of overexpressed uncoupling proteins (UCPs) in the Warburg effect [11], several new ideas have recently emerged indicating that alterations in the glycolytic pathway itself may be equally or even more important.

In this regard, it was suggested that pyruvate kinase M2 (PKM2) or hexokinase 2 might be the key mediators of aerobic glycolysis and promote tumor growth at least in certain types of tumors [12,13]. Moreover, PKM2 was shown to function as a co-activator of hypoxia-inducible factor 1α (HIF1α). However, new concepts that point to how epigenetic alterations may orchestrate changes in glucose metabolism in cancer cells appear to be especially promising. Epigenetic mechanisms are responsible for the regulation of gene expression through the covalent modifications of DNA and histones, which affect the chromatin architecture. Among the many proteins that are engaged in the regulation of covalent histone modifications, sirtuins might play a particularly important role in their relevance to metabolic regulation [14,15]. On the other hand, these proteins may also act on non-histone targets and thus may directly modulate protein activity *via* non-epigenetic mechanisms. In this review we describe the role of sirtuins in cancer energetic metabolism and the possible application of their modulation in therapeutic or chemopreventive strategies.

Epigenetics and cancer metabolism

It is becoming evident that epigenetic changes may substantially contribute to the Warburg effect in addition to the mechanisms that are related to genetic changes and aberrant gene expression [16]. Two changes that are integral to epigenetic transcriptional control are DNA methylation and covalent modifications of histone proteins, particularly their acetylation.

In this regard, it was found that fructose-1,6-bisphosphatase 1 (FBP1), which under physiological conditions can suppress glycolysis by reducing the level of fructose-1,6-bisphosphate, is epigenetically silenced as a result of its promoter methylation in gastric and breast cancer cells [17,18].

Interestingly, FBP1 is down-regulated in oncogenic Ras-transformed cells, gastric cancer cell lines as well as primary gastric carcinomas. Restoration of FBP1 leads to inhibition of cancer cell growth, although it is unclear whether such a growth-inhibitory effect depends solely on its glycolysis suppression function. Nevertheless, the epigenetic silencing of FBP1 could confer certain growth advantages in tumor cells, thus playing an important role in tumor progression. Indeed, promoter hypermethylation of *FBP1* is associated with poor outcome in gastric cancer patients. Moreover, NF-κB activity, which is indispensable to the Ras-mediated transformation, seems to be essential in the maintenance of epigenetic silencing of *FBP1*. The NF-κB family of transcription factors plays a crucial role in the regulation of inflammatory and immune responses, cell survival, cell proliferation, and in carcinogenesis [19].

NF-κB-dependent silencing of *FBP1* thus represents a new link between inflammation and carcinogenesis. The major activator of NF-κB, *i.e.* TNFα, is increased in a tumor-permissive microenvironment. By promoting NF-κB activation and consequent *FBP1* silencing, signals from the tumor microenvironment can switch the oxygen-dependent glucose metabolism into oxygen-independent glycolysis. Together with its well-known anti-apoptotic functions, this novel function of NF-κB can promote the survival and proliferation of initiated tumor cells in a hypoxic microenvironment, thus facilitating tumor development.

Changes in the profile of covalent modifications of histone proteins also play an important role in the alteration of gene expression that leads to carcinogenesis. Histone proteins, which build the nucleosome core, contain a globular C-terminal domain and an unstructured N-terminal tail. The N-terminal tails of histones can undergo a variety of posttranslational covalent modifications, including methylation, acetylation, ubiquitylation, sumoylation, and phosphorylation on specific amino acid residues. Histone modifications work by either changing the accessibility of chromatin or by recruiting and/or occluding non-histone effector proteins, which decode the message encoded by the modification patterns. Unlike DNA methylation, histone modifications can lead to either activation or repression of transcription, which depends on the localization of the residue and the type of modification; for example, lysine acetylation correlates with transcriptional

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